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Fracture rates with monthly oral ibandronate and weekly bisphosphonates: the eValuation of IBandronate Efficacy (VIBE) database fracture study

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INTRODUCTION

- Low adherence rates to weekly oral bisphosphonate (BP) treatment for postmenopausal osteoporosis have prompted the development of regimens with extended dosing intervals to try to enhance adherence and persistence
- A meta-analysis of the ibandronate phase III clinical trial program showed that ibandronate treatment at doses including monthly oral ibandronate 150 mg reduces the risk of nonvertebral fractures (NVFs) and all clinical fractures compared with placebo[1]
- In the MOTION study, the bone mineral density (BMD) response to monthly oral ibandronate 150 mg was shown to be similar to weekly alendronate 70 mg,[2] but further data comparing the efficacy of weekly and monthly BPs in a real-world setting are warranted
- Database analyses allow the assessment of treatments in normal clinical practice, avoiding the effect of trial participation on outcomes and allowing evaluation of agents in a population with a broader range of characteristics than typically permitted in a randomized clinical trial. Thus, findings from database studies, although subject to more confounding variables, provide a valuable insight into the real-world use of treatments

OBJECTIVE

- The objective of this database study was to evaluate fracture rates in patients treated with monthly ibandronate compared with weekly BPs in clinical practice. Two study questions were addressed:
  - In patients adherent to treatment, is there a difference in fracture rates for monthly ibandronate compared with weekly BPs?
  - Is there a difference in fracture rates in patients prescribed monthly ibandronate or weekly BPs, irrespective of adherence?

METHODS

Study design

- The eValuation of IBandronate Efficacy (VIBE) study was a retrospective claims database study
- Data sources included eligibility, pharmacy claims, and medical claims data from:
  - the i3 (Eden Prairie, MN) research database (for any given year, includes 14 million employees with retail pharmacy and medical benefits and 8 million with medical benefits only)
  - the i3 Innovus IMPACT database (includes approximately 75.7 million unique lives)

Study population

Inclusion criteria

- Women aged ≥45 years, newly prescribed monthly ibandronate or a weekly oral BP (alendronate [35 mg or 70 mg] or risedronate [35 mg]) between April 1, 2005 and December 31, 2005
- Continuous health plan eligibility for 6 months prior to the index date (pre-index period), and at least 3 months after the index date

Exclusion criteria

- BP dispensing during the pre-index period
- Malignant cancer (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 140.xx – 208.xx) during the pre-index period or Paget's disease (ICD-9-CM code 731.0) at any time during the study

Efficacy assessments

- The following patient characteristics were assessed during the pre-index period: number of concomitant medications, gastrointestinal medication use, estrogen use, other non-estrogen antiosteoporotic medication use (calcitonin or raloxifene), glucocorticoid use, outpatient visits, hospitalizations, fracture history, and age
- Other patient characteristics were assessed via pre-index claims data using ICD-9-CM and Current Procedural Terminology (CPT) codes for osteoporosis, osteopenia, gastrointestinal, or rheumatoid arthritis diagnoses, or bone densitometry
- Outcomes were fractures identified via ICD-9-CM codes
- Fractures were considered new if there was no evidence of a fracture at the same site during the pre-index period

Statistical analyses

- Primary outcome variables were the rates of hip fractures, NVFs, vertebral fractures, and all fractures in patients receiving monthly oral ibandronate compared with patients receiving weekly BPs. Vertebral fractures were not validated by presence of a code for spinal x-ray
- Baseline and outcome measures were analyzed descriptively. The chi-square test was used to compare dichotomous variables and the Wilcoxon rank sum test was used to compare continuous variables
- Fracture rates were compared using time-to-event analysis with Cox proportional hazards models to estimate the relative risk (hazard rate) of fracture for monthly ibandronate vs weekly BPs, controlling for potential fracture risk factors
- Potential confounding factors were identified from the literature and osteoporosis experts and used to create candidate variables for each patient during the 6-month pre-index period
- Candidate variables included age, number of therapeutic classes for which a patient received prescriptions, use of gastrointestinal medications (proton pump inhibitors, H2 antagonists, or cytoprotectives), estrogens, non-estrogen antiosteoporotic medications (calcitonin or raloxifene), glucocorticoids, number of outpatient visits, number of hospital admissions, presence of a diagnosis code for osteoporosis or osteopenia, use of bone densitometry procedures, and presence of a fracture
- All candidate variables were entered into the initial Cox models; forward stepwise regression was used to identify variables that contributed to significant improvements in model performance. Final models retained only those variables that made a significant difference in model performance. Conclusions remained the same when additional clinical variables were added to the model
- Prior to the study, a difference of 0.2% to 0.3% in NVF or hip fracture rates was hypothesized between monthly ibandronate and weekly BP patients. A total of at least 32,000 patients was required to be included in the analysis to demonstrate this difference with a power of 80%
- Analysis populations:
  - ***Primary analysis*** (adherent patients, analogous to per-protocol population in a clinical trial). Excludes patients who discontinued treatment within the first 90 days from the index date (defined as a 45-day prescription gap for monthly ibandronate, and a 30-day gap for weekly BPs). Data were censored at the date of: fracture, 12 months from the index date, end of health plan enrollment, BP brand switch, regimen switch, or treatment discontinuation (discontinuation date defined as last dispensing date plus days supplied plus 45 days for monthly ibandronate or 30 days for weekly BPs), whichever came first
  - ***Secondary analysis*** (all patients, analogous to intent-to-treat population in a clinical trial). Includes all patients initiating study BP treatment, regardless of adherence to treatment
- ***Sensitivity analyses*** were conducted based on the primary analysis, excluding patients with codes for the following in the pre-index period:
  - estrogen or non-estrogen osteoporosis medication
  - glucocorticoids
  - fracture
  - gastrointestinal medications
  - glucocorticoids and/or osteopenia
- Further sensitivity analyses were conducted varying the requirement for adherence to treatment

RESULTS

Patient demographics and disease characteristics

- Details of the analysis populations are shown in **Table 1**
- The primary analysis population included 64,182 patients (ibandronate n=7345; weekly BPs n=56,837). Mean follow-up was approximately 7 months in both treatment groups. Patient demographic and disease characteristics are presented in **Table 2**

Table 1. Identification of analysis populations from the database

Group/analysis population	i3 research database n	i3 IMPACT database n	Total n
Secondary analysis (all patients)	25,181	66,417	91,598
Primary analysis (adherent patients)	17,434	46,748	64,182

Table 2. Demographics and disease characteristics (primary analysis population)

Characteristic	Monthly therapy (n=7345)	Weekly therapy (n=56,837)	*P* value
Duration of observation, d, mean ± SD (median)	222.8 ± 94.1 (199)	217.8 ± 98.3 (196)	0.002
Age, y, mean ± SD (median)	60.1 ± 8.6 (59)	60.5 ± 8.8 (59)	0.002
No. of concomitant medications in pre-index period, mean ± SD (median)	6.1 ± 4.9 (5)	5.0 ± 5.3 (4)	<0.001
Medications in pre-index period, n (%)			
GI	1732 (23.6)	9392 (16.5)	<0.001
Estrogen	1829 (24.9)	10,919 (19.2)	<0.001
Other non-estrogen antiosteoporosis	794 (10.8)	3372 (5.9)	<0.001
Glucocorticoid	914 (12.4)	5572 (9.8)	<0.001
No. of outpatient visits in pre-index period, mean ± SD (median)	15.9 ± 16.9 (11)	15.0 ± 17.2 (10)	<0.001
Medical history in pre-index period, n (%)			
Hospitalization	393 (5.4)	3135 (5.5)	0.559
Osteoporosis diagnosis	2952 (40.2)	20,158 (35.5)	<0.001
Osteopenia diagnosis	31 (0.4)	170 (0.3)	0.076
Bone densitometry procedure	4131 (56.2)	31,415 (55.3)	0.116
GI diagnosis	1606 (21.9)	9454 (16.6)	<0.001
Rheumatoid arthritis diagnosis	280 (3.8)	1611 (2.8)	<0.001
Fracture history	262 (3.6)	2113 (3.7)	0.520

GI = gastrointestinal; SD = standard deviation.

Study sponsored by Roche and GlaxoSmithKline

Primary analysis

- Fracture rates were low in both the monthly ibandronate and weekly BPs treatment groups (NVF: monthly 95 patients [1.29%], weekly 738 [1.30%]; hip: monthly 15 [0.20%], weekly 106 [0.19%]; vertebral: monthly 8 [0.11%], weekly 135 [0.24%]; all fractures: monthly 103 [1.40%], weekly 858 [1.51%]; **Figure 1**)
- Rates of hip fractures, NVFs, and all fractures were not significantly different between the 2 treatment groups (**Figure 2**)
- Ibandronate patients had a statistically lower vertebral fracture rate than weekly BP patients (adjusted relative risk, 0.36; 95% confidence interval [CI], 0.18–0.75; *P*=0.006) (**Figure 2**)

Secondary analysis

- When data from all patients were analyzed, the rates of hip fractures, NVFs, vertebral fractures, and all fractures were not significantly different between patients receiving monthly ibandronate and patients receiving weekly BPs (**Figure 3**)

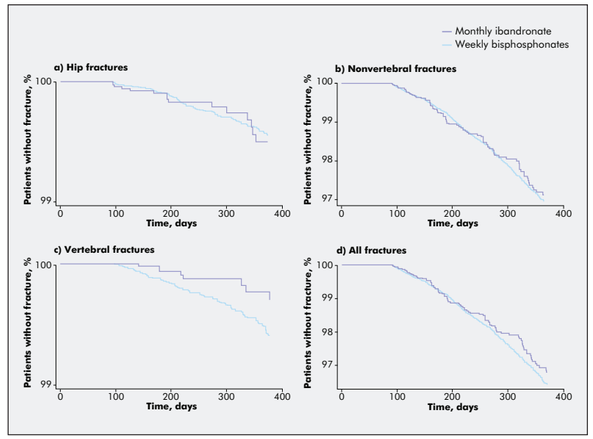
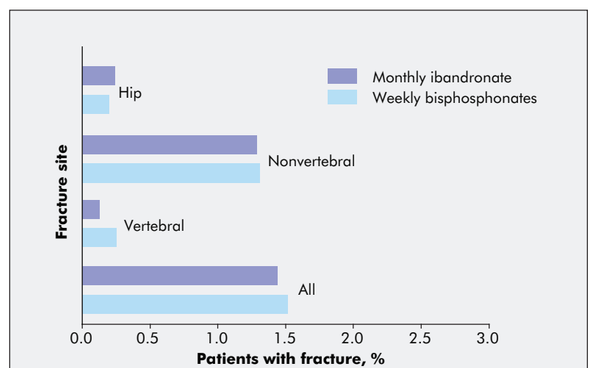


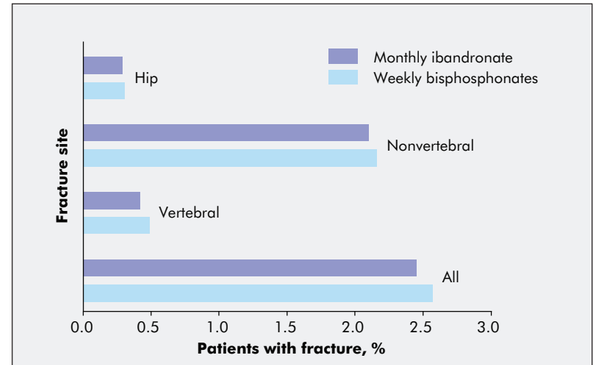
Figure 1. Time to fracture (primary analysis; monthly n=7345, weekly n=56,837)



Fracture type	Crude rate ratio	Adjusted rate ratio (95% CI)	*P* value
Hip	1.07	1.06 (0.61–1.83)	0.840
Nonvertebral	0.97	0.88 (0.71–1.09)	0.255
Vertebral	0.44	0.36 (0.18–0.75)	0.006
All	0.90	0.82 (0.66–1.00)	0.052

CI = confidence interval.

Figure 2. Fracture incidence (primary analysis; monthly n=7345, weekly n=56,837)



Fracture type	Crude rate ratio	Adjusted rate ratio (95% CI)	*P* value
Hip	1.00	1.03 (0.70–1.51)	0.884
Nonvertebral	1.06	1.01 (0.87–1.17)	0.904
Vertebral	0.93	0.86 (0.62–1.19)	0.361
All	1.04	0.98 (0.86–1.19)	0.807

CI = confidence interval.

Figure 3. Fracture incidence (secondary analysis; monthly n=10,020, weekly n=81,578)

Sensitivity analyses

- Rates of hip fractures and NVFs were not significantly different between the 2 treatment groups in all sensitivity analyses
- Ibandronate patients had a statistically lower vertebral fracture rate compared with weekly BP patients in all sensitivity analyses, except the analysis including patients who were not adherent to treatment for at least 90 days after the index date

Limitations

- As this was a retrospective cohort study, there are limitations to the data available:
  - The presence of a claim does not indicate that the medication was taken or taken correctly
  - No data are available on prescriptions filled without claims being made or samples provided by physicians
  - The presence of a diagnosis code does not necessarily indicate presence of the disease (the diagnosis may be incorrectly coded or coded as rule-out criteria)
  - Limited data are available on the nature of the fractures, or whether they were traumatic or atraumatic
  - Treatment selection may be influenced by factors that are not recorded in the database and that could influence outcomes
  - Data were not available on dual-energy x-ray absorptiometry, fractures before the pre-index period, or fracture risk factors such as smoking or alcohol use
- The analysis controlled for baseline characteristics; however, in a real-life study it is possible that unidentified baseline differences existed which were not accounted for
- The population studied was a relatively young group, not at high risk for fractures, as reflected by the low proportion of patients experiencing fractures during follow-up

CONCLUSIONS

- These findings suggest that in a real-life clinical setting, at 12 months from treatment initiation, the risk of hip fractures or NVFs is similar in patients who have received monthly ibandronate or weekly BPs
- The sensitivity analyses conducted generally supported the findings of the primary analysis

REFERENCES

1. Harris ST, et al. *Curr Med Res Opin*. 2008;24:237-45.
2. Miller PD, et al. *Curr Med Res Opin*. 2008;24:207-13.